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We summarize here the results presented and subsequent discussion from the meeting on Integrating Hebbian and Homeostatic Plasticity at the Royal Society

in April 2016. We first outline the major themes and results presented at the meeting. We next provide a synopsis of the outstanding questions that emerged from the discussion at the end of the meeting and finally suggest potential directions of research that we believe are most promising to develop an understanding of how these two forms of plasticity interact to facilitate functional changes in the brain.

One of the more pleasant and surprising take away messages from the meeting was the overall agreement between the conclusions drawn from the data in numerous preparations, brain areas and approaches to alter activity patterns and levels. We found that there are several general principles that repeatedly emerge across approaches.

1) Stabilizing mechanisms are likely necessary to keep Hebbian changes to the system under control, otherwise activity becomes extreme, either too high or low.

2) Multiple mechanisms of both Hebbian and homeostatic plasticity are repeatedly observed across varied experimental and theoretical work.

3) These mechanisms can stabilize numerous cellular and network parameters – overall firing rate, sub-threshold activity and individual synaptic weights.

4) Hebbian and homeostatic mechanisms have striking similarities observed among different brain regions *in vivo* and *in vitro*, suggesting that many of these mechanisms may be common across brain regions.

We will review these general principles in turn, and then discuss important future directions to address inconsistencies and missing points in our current understanding.

The necessity of stabilizing mechanisms

One question that is frequently raised outside of the homeostatic plasticity field is whether or not these stabilizing mechanisms are actually necessary for proper brain function. This question has been repeatedly addressed by theorists and

modelers and their work typically indicates that without some form of stabilization of firing rates or synaptic weights, network models that can store memory patterns in recurrent synaptic strength become unstable, typically in the direction of activity being too high (Litwin-Kumar and Doiron, 2014; Marder and Prinz, 2002; Tetzlaff et al., 2011; Zenke et al., 2013). These runaway increases in activity emerge from the fact that most Hebbian strengthening mechanisms are dependent on coincident firing between the pre- and post-synaptic neurons and this process involves a positive feedback loop: namely, the more frequent coincident activity in a group of neurons is, the more likely that synapses connecting these neurons are strengthened. These strengthened synapses further increase coincident activity within the group and very quickly, in a positive feedback loop, activity pathologically increases.

Mechanisms of homeostatic stabilization

If some form of stability is necessary, what mechanisms may provide this stability and what properties do these mechanisms have? Three major mechanisms were reported at this meeting, although this list is not comprehensive of the possible mechanisms, nor are they mutually exclusive.

1. Synaptic scaling
2. Changes to inhibition through inhibitory cell activity or the strength and number of inhibitory synapses onto excitatory cells
3. Constraints and intrinsic fluctuations of spine size dynamics (which likely reflects changes in synaptic strength and thus overlaps to some degree with stabilizing mechanisms)

Synaptic scaling

The first experimental evidence for synaptic scaling (Turrigiano et al., 1998) demonstrated that in response to a decrease in firing rate, the synaptic weights of the population of the excitatory post-synapses on a cell were increasingly scaled in size by a multiplicative factor, such that the relative weights of the synapses were preserved (and vice-versa in response to an increase in activity). Many studies have confirmed this original result *in vitro* (Turrigiano Position

Paper in this issue), as well as *ex-vivo* in acute slices prepared from both juvenile and adult animals that had previously undergone *in vivo* deprivation (Desai et al., 2002; Gainey et al., 2015, 2009; Goel and Lee, 2007; Hengen et al., 2013; Keck et al., 2013; Maffei and Turrigiano, 2008; Ranson et al., 2012). Synaptic scaling does have layer specific properties in cortex, where scaling in layer 4 is limited to early development (Desai et al., 2002), but layer 5 (Greenhill et al., 2015; Keck et al., 2013) and layer 2/3 (Goel and Lee, 2007) can scale throughout adulthood. Numerous molecular mechanisms have been implicated in mediating synaptic scaling, including TNF-alpha (Greenhill et al., 2015; Kaneko et al., 2008b; Stellwagen and Malenka, 2006), which may be regulated via astrocytic activity and NMDA receptor expression (Haydon and Nedergaard, 2015), Retinoic acid (Arendt et al., 2015), among many others (for a review see (Siddoway et al., 2014; Turrigiano, 2012)). Increases in TNF-alpha has been reported to increase and decrease the density of AMPA and GABAA receptors, respectively, in the plasma-membrane (Stellwagen and Malenka, 2006).

Rapid changes to levels of inhibition

In addition to synaptic scaling, which takes several days *in vivo*, altering the levels of inhibition and generally the balance between excitation and inhibition on a given cell is a frequently observed mechanism used to stabilize activity in the brain. Reducing the levels of inhibition onto excitatory neurons is consistently observed following loss of input in cortex (Chen et al., 2012, 2011; Goel and Lee, 2007; Keck et al., 2011; Kuhlman et al., 2013; Li et al., 2014; van Versendaal et al., 2012) and has been hypothesized to be a first step in circuit reorganization following input loss (Sammons and Keck, 2015). Changes in inhibition can occur via a reduction in the number (Barnes et al., 2015; Chen et al., 2012; Hartman et al., 2006; Keck et al., 2013, 2011; Kreczko et al., 2009; Li et al., 2014; van Versendaal et al., 2012; van Versendaal and Levelt, 2016) or strength of inhibitory synapses onto excitatory cells, as well as a reduction in the firing rate of the inhibitory neurons following deprivation either temporarily during development (Hengen et al., 2013; Kaneko and Stryker, 2014) or for longer time courses in adulthood (Barnes et al., 2015). Changes in inhibitory tone may be modulated via astrocytes (Lalo et al., 2014) or NMDA receptor input

(Zhang et al., 2008). Changing the activity of inhibitory neurons provides an important homeostatic mechanism by which activity levels can be rapidly (within seconds) adjusted through the increase or decrease in the firing rate of inhibitory neurons to prevent short-term increases in activity levels that would be associated with pathological activity like seizures; however, recent work suggests that minimizing changes to inhibition helps maintain temporal coding in the network, which is shaped by the inhibitory circuit (Lee et al., in this issue), so some maintenance of inhibitory tone is likely essential for the circuit. Adjusting synaptic strength or neuronal excitability occurs over much longer time courses of hours (Turrigianio Position Paper in this issue), which would be much too slow to account for activity peaks that would potentially cause pathological over-excitation.

Changes in spine sizes

Dendritic spines - the location of excitatory synapses - can change in size in response to long-term potentiation (LTP) and long-term depression (LTD) (Bosch et al., 2014; Matsuzaki et al., 2004) or while synaptic scaling occurs (Keck et al., 2013; Wallace and Bear, 2004), in a way that likely at least partially reflects changes in synaptic strength. Limits on the sizes of dendritic spines provides yet another mechanism by which stability can be achieved in the brain. Given that spine size has a maximum (Matsuzaki et al., 2004), synapses cannot be strengthened indefinitely (O'Donnell et al., 2011). Furthermore, spine size is not only controlled by LTP, LTD, and during synaptic scaling, but also by intrinsic fluctuations that happen even in the absence of neural activity (Yasumatsu et al., 2008). Fluctuations of spine size increase approximately linearly with the initial size and this relationship explains the steady state distribution of spine sizes with a long tail (Loewenstein et al., 2011; Yasumatsu et al., 2008). A simulation study of recurrently connected networks suggests that such fluctuations can stabilize network activity by constitutively restoring the spine size distribution close to the physiological steady state distribution, while ongoing Hebbian plasticity forms and maintains cell assemblies (Humble et al., 2016, 2014). In addition to changes in the structural size of synapses, the properties and activation of NMDA receptors within a synapse have been implicated in

monitoring overall changes to activity levels (Lisman Position Paper in this issue).

Parameters of homeostatic balance

In order for these mechanisms to be truly homeostatic, they need to restore cellular and synaptic activity levels back closely to pre-perturbation levels. What characteristics of the circuit are being stabilized by these mechanisms that makes this process homeostatic? There is experimental evidence for three balance parameters: firing rate homeostasis, subthreshold activity homeostasis, and synaptic weight homeostasis and any of these three parameters, when incorporated into the appropriate theoretical model may stabilize the network to prevent pathological neuronal dynamics or learning (Bienenstock et al., 1982; Clopath et al., 2010; Fiete et al., 2010; Harnack et al., 2015; Litwin-Kumar and Doiron, 2014; MacKay et al., 1994; Oja, 1982; Tetzlaff et al., 2011; Toyoizumi et al., 2014, 2013; Toyoizumi and Miller, 2009; van Rossum et al., 2000; von der Malsburg, 1973; Yger and Gilson, 2015; Zenke et al., 2013).

First, firing rate homeostasis was initially described with the first experimental evidence of synaptic scaling (Turrigiano et al., 1998) and altering cellular (Burrone et al., 2002) and network firing rate has consistently evoked a response of the induction of homeostatic mechanisms (Barnes et al., 2015; Desai et al., 2002; Hengen et al., 2016, 2013; Keck et al., 2013; Turrigiano et al., 1998). Several studies have now demonstrated that neurons will recover their firing rates *in vitro* (Burrone et al., 2002; Turrigiano et al., 1998) and *in vivo* (Barnes et al., 2015; Hengen et al., 2016, 2013; Keck et al., 2013), in parallel with the induction of homeostatic mechanisms, and that neurons in the developing visual cortex have a firing rate set point that they return to after deprivation (Hengen et al., 2016). Recent work has also suggested that subthreshold changes in activity levels are sufficient to induce homeostatic mechanisms, specifically synaptic scaling (Fong et al., 2015), although whether these changes restore subthreshold activity levels remains unexplored.

The sliding threshold proposed in the BCM theory would provide an additional method by in which firing rates could be homeostatically modulated (Bienenstock et al., 1982). By rapidly and superlinearly increasing the threshold

for inducing LTP as background firing rates get higher and decreasing the threshold as background firing rates are lower, synapses would be unlikely to be strengthened if activity rates were too high. This sliding threshold model would provide an internal mechanism by which activity levels never become too high or too low. There is considerable experimental evidence for the existence of such a sliding threshold, including both evidence of structural and functional plasticity, which has been reviewed extensively elsewhere (Cooper and Bear, 2012). However, the time-scale of the sliding threshold is an important factor for determining the stability (Yeung et al., 2004) and the theoretically predicted supralinear relation of the threshold with background firing rate is awaiting further experimental evidences.

Homeostasis of synaptic weights (Davis and Bezprozvanny, 2001; Shah and Crair, 2008) provides an intriguing alternative to homeostatic regulation of firing rate, since constraining synaptic weights would be an effective mechanism for guiding activity dependent circuit organization. Recent work (Bourne and Harris, 2011) suggests that overall synaptic weight is conserved on a dendritic branch, thus preventing too much activity that would result from an over strengthening of synapses.

Interactions with mechanisms of Hebbian plasticity

Hebbian mechanisms have been largely reviewed elsewhere and are well-summarized in one of the position papers in this issue (Lisman Position Paper in this issue). An important feature of these Hebbian mechanisms in relation to their interaction with homeostatic mechanisms, is that their time courses and effects can be wildly different. Hebbian mechanisms are synapse specific and can be implemented over milliseconds (short-term plasticity) to hours (long-term LTP/LTD), whereas synaptic scaling occurs cell-wide and can take a few days to commence *in vivo* (Turrigiano Position Paper in this issue, Greenhill et al., 2015; Kaneko et al., 2008a, 2008b). Hence, there is a considerable disparity between the effects and time courses between these homeostatic and Hebbian mechanisms. Theoretical work suggests that separating the expression mechanisms (e.g. spine size or membrane AMPA density) for these two processes can minimize their interface and prevent oscillatory instability of

synaptic weight, which could result from the delay in the negative feedback of the homeostatic plasticity (Toyoizumi et al., 2014). However, since multiple time scales are involved in both Hebbian and homeostatic mechanisms, further experimental characterization of these disparate time courses is essential going forward (Gerster Position Paper in this issue).

Similarities across brain regions in vivo

For both Hebbian and homeostatic mechanisms, there are striking similarities of plasticity responses across numerous regions of cortex and varying plasticity induction paradigms (for a review see Gainey and Feldman in this issue). Starting with homeostatic plasticity, similar mechanisms are invoked following sensory deprivation in both somatosensory (Greenhill et al., 2015; Li et al., 2014) and visual cortices (Chen et al., 2012; Desai et al., 2002; Goel and Lee, 2007; Greenhill et al., 2015; Hengen et al., 2016, 2013; Keck et al., 2011, 2013; Maffei and Turrigiano, 2008; Ranson et al., 2012; van Versendaal et al., 2012), where decreases in inhibition precede any Hebbian mechanisms and synaptic scaling is reliably induced in a layer specific manner (Bender et al., 2006; Desai et al., 2002; Li et al., 2014). Hebbian mechanisms have correlates in synaptic structural plasticity, in which long-term potentiation is correlated with the formation of new spines (Engert and Bonhoeffer, 1999; Maletic-Savatic et al., 1999) and long-term depression is associated with the loss of pre-existing spines (Nagerl et al., 2004). The *in vivo* upregulation of spine dynamics have been observed following sensory deprivation in somatosensory cortex (Holtmaat et al., 2005, 2006; Trachtenberg et al., 2002; Zuo et al., 2005), olfactory cortex (Kopel et al., 2012; Mizrahi, 2007), auditory cortex (Moczulska et al., 2013) and visual cortex (Grutzendler et al., 2002; Hofer et al., 2009; Holtmaat et al., 2005; Keck et al., 2008; Zuo et al., 2005) and following learning in motor cortex (Fu et al., 2012; Xu et al., 2009; Yang et al., 2009), where the memory of the learned motor task depends on the newly formed synapses (Hayashi-Takagi et al., 2015). The interactions between Hebbian and homeostatic plasticity have largely been described in the visual cortex following monocular deprivation, where it is proposed that the Hebbian process of long-term depression (Rittenhouse et al., 1999) is followed by an increase in synapse strength (Stryker Position Paper in

this issue). The similarities across somatosensory, motor and visual cortices may suggest that mechanisms of homeostatic and Hebbian plasticity are conserved across brain regions, at least in cortex.

Future directions and major questions going forward

While a number of general experimental and theoretical properties emerged from this meeting, a large number of outstanding questions remain to be answered related to how Hebbian and homeostatic plasticity interact to facilitate normal function and circuit plasticity. Here, we outline the major questions that were discussed at the meeting.

Interactions between theoretical and experimental approaches

One area for potential expansion is in the interaction between theory and experiments and within experimental work between detailed mechanistic work and more general behavioral/*in vivo* work. Linking results at different levels of investigation, while a general issue in neuroscience, is particularly important to understanding the interaction between homeostatic and Hebbian plasticity. Work in this field has to some degree diverged into two categories. First, systems approaches that include *in vivo* work done in anaesthetized or behaving animals (Barnes et al., 2015; Greenhill et al., 2015; Hengen et al., 2016, 2013, Kaneko et al., 2008a, 2008b; Keck et al., 2013; Ranson et al., 2012) and theoretical work that models the overall dynamics of the systems (Bienenstock et al., 1982; Clopath et al., 2010; Fiete et al., 2010; Harnack et al., 2015; Lim et al., 2015; Litwin-Kumar and Doiron, 2014; MacKay et al., 1994; Oja, 1982; Tetzlaff et al., 2011; Toyoizumi et al., 2014, 2013; Toyoizumi and Miller, 2009; von der Malsburg, 1973; Yger and Gilson, 2015; Zenke et al., 2013). These systems studies importantly provide insight into mechanisms that are employed in the intact brain and how activity levels are affected by these mechanisms, but have limited control of other secondary inputs from outside of the main pathways studied that may provide compensatory mechanisms. So these experiments often cannot pinpoint the exact inputs and brain states affecting activity levels or the relative changes to the pre- and post-synaptic cells, particularly in behavioral experiments where the animals are free to experience their environment

(somewhat) naturally. These limitations make it difficult for the *in vivo* experiments to provide detailed information – for example, the originating brain area from which inputs are lost following deprivation - to these theoretical studies, where the localization of activity changes (pre- or post-synaptically) and knowledge of the rules for circuit reorganization would be useful. As a result, predictions from theory to *in vivo* experiments and vice-versa thus far are limited to qualitative aspects. The second focus of experiments is at the molecular and cellular experimental level, where numerous molecular mechanisms have been described to play a role in both homeostatic (Arendt et al., 2015; Stellwagen and Malenka, 2006; Turrigiano, 2012) and Hebbian (Sweatt, 2016) plasticity, as well as their interactions (Turrigiano and Nelson, 2000; Vitureira and Goda, 2013). While new molecular and systems tools make it easier to link these molecular and cellular mechanisms to *in vivo* experiments, for example through the use of Cre-dependent expression of target mechanisms, the brain's redundancy, evidenced by observed compensatory pathways, can make it difficult at times to tease apart the precise roles of individual molecules in the healthy brain. Importantly, the theory and molecular experiments may have greater potential for interaction, which to date has been largely unexplored, as theoretical models can predict the time course and spatial scale of action of a molecular cue that would be necessary to facilitate plasticity (Urakubo et al., 2008). Given our knowledge of these potential molecular cues *in vivo* and *in vitro*, this is one area where theoretical work could be instructive in linking the systems experiments with the molecular and cellular experiments. Similarly, mechanisms involved in the recovery of individual neurons tuning following sensory deprivation *in vivo* (Barnes et al., 2015; Greenhill et al., 2015; Hengen et al., 2016, 2013, Kaneko et al., 2008a, 2008b; Keck et al., 2013; Ranson et al., 2012; Rose et al., 2016) could be explained via theoretical work. Theoretical models using attractor dynamics or hidden states (Fusi et al., 2005; Ziegler et al., 2015) could be implemented to better understand how interactions between individual cells and the network of cells facilitate the recovery of activity following deprivation and maintain the same properties of individual cells from prior to deprivation (Rose et al., 2016; Rose and Clopath in this issue). Overall, better interaction between molecular/cellular and systems level experiments

and theory will be critical to understand the underlying details of the mechanisms of plasticity and how they are implemented *in vivo*.

Time scales of homeostatic and Hebbian plasticity interactions

One of the important questions to emerge from this meeting is how the disparate time scales of homeostatic and Hebbian plasticity could interact to maintain firing rate homeostasis and overall stability. The main issue emerges from the fact that homeostatic plasticity mechanisms occur over a very slow time course, hours at their fastest (Turrigiano, 2008), whereas Hebbian plasticity can occur over a period of seconds to minutes (Lisman Position Paper in this issue). Given that recurrent excitation and synaptic strengthening can happen very quickly, the stability mechanisms described by the classic homeostatic mechanisms are not rapid enough to stop run-away excitation. Theoretical models have described approaches that facilitate network stability with these disparate time courses (Toyoizumi et al., 2014), but at the same time suggested the need for a fast down-regulating homeostatic mechanism to avoid seizure like activity (Gerstner Position Paper in this issue). One possible explanation for this discrepancy between theory and experiment is that a majority of experiments focus on up-regulating homeostatic mechanisms that occur after input loss and a decrease in activity levels. With the up-regulation of activity, a longer time course might be sensible, given that short-term deceases in activity levels could be for a number of reasons – for example in visual cortex, entering a dark room could potentially reduce visual cortical activity. If activity returns when you enter the light again, having quickly up-regulated the strengths of synapses in response to the dark stimulus would result in too much activity with light stimulation. Hence, up-regulating homeostatic mechanisms may occur over a longer time course to ensure that the reduction of activity is (semi) permanent before the system compensates for these changes. Additionally, using a wide dynamic range of activity is optimal for information coding in the brain (Laughlin, 1981). Therefore, adjusting the firing rate set point too quickly would minimize the range of activity patterns and rates that encode input to a cell and in theory reduce its computational power (Toyoizumi et al., 2014). As a result,

homeostatic adjustments may be slower when activity levels are not dangerous for toxicity.

These results could suggest the potential for a non-symmetric up- and down-regulation, like that observed for LTP and LTD, where potentiation can occur more reliably and quickly (Lisman Position Paper in this issue). As for experimental evidence for homeostatic-down regulation, work in cortical cultures indicates that it is possible (Siddoway et al., 2014; Turrigiano et al., 1998), but approaches for extended increases in activity *in vivo* remain elusive. The difficulty of maintaining heightened activity *in vivo* for extended periods of time, may speak to the existence of a fast down-regulating homeostatic mechanism that has yet to be experimentally observed. The relevant time scales for both homeostatic and Hebbian plasticity mechanisms remain an unanswered question and a critical one for understanding their interactions.

Spatial scales of synaptic plasticity and homeostatic set points

Similar to the issue of time scales, understanding the spatial scales of both homeostatic and Hebbian mechanisms are critical for considering their interactions. Homeostatic mechanisms can be implemented at the level of individual synapses (Lee et al., 2010), dendritic branches (Bourne and Harris, 2011; Cichon and Gan, 2015; Losonczy et al., 2008; Makara et al., 2009; Yu and Goda, 2009), single cells (Burrone et al., 2002; Turrigiano et al., 1998) and the network (Barnes et al., 2015), but obviously the interactions between these spatial scales will play an important role in overall firing rate homeostasis. For example, if the activity at all individual synapses is homeostatically regulated, then activity in dendritic branches, single cells and the network would be affected (and somewhat regulated) by that local regulation. The spatial scale of plasticity implementation is another area where molecular and cellular experiments may match up well with theory. Many of the more local implementations (individual synapses, dendritic branches, and volume surrounding glial cells) of plasticity mechanisms may be governed by second messengers and molecules acting in these local environments. Thus, examining the relevant spatial scales in theoretical models (Sweeney et al., 2015) may offer

predictions for the spatial and temporal characteristics of molecules that would potentially facilitate some of the activity effects observed in these models and in the *in vivo* data.

Understanding the spatial scales of the implementation of plasticity mechanisms may also provide insight into the spatial scales for the set points of activity or synaptic weight to which these homeostatic mechanisms are returning the synapse, branch, cell or network. Whether homeostatic mechanisms are balancing spontaneous firing rate, evoked firing rate, a combination of those two (Hengen et al., 2016), the weight of excitatory synapses (Bourne and Harris, 2011) or subthreshold activity (Fong et al., 2015; O'Leary et al., 2014) remains unclear. One possibility is that there may be multiple spatial set points and the specific set point is regulated by homeostatic mechanisms implemented at that spatial scale. So balancing neuronal firing rates in the network would occur via network level homeostatic mechanisms, and balancing synaptic weights in a dendrite would occur through dendritic branch level implementation of homeostatic mechanisms. How and when these different set points and homeostatic mechanisms are implemented at these spatial scales remain unanswered questions and are important for understanding how these plasticity mechanisms occur *in vivo*.

How do mechanisms interact?

Numerous homeostatic plasticity mechanisms (synaptic scaling, changes to the balance between excitation and inhibition, changes in excitability, spine size fluctuations; Turrigiano, 2008) and Hebbian mechanisms (short term plasticity, short LTP, long LTP, LTD; Lisman Position Paper in this issue) have been described. These mechanisms have largely been studied in isolation and there is limited understanding of how these mechanisms may interact. For example, are multiple homeostatic mechanisms engaged in an individual cell following input loss? If so, do they all have the same threshold of activity change? Previous work (Maffei and Turrigiano, 2008) indicates that different forms of deprivation induce different homeostatic mechanisms in layer 2/3 of the visual cortex *ex-vivo*, suggesting that the exact nature of changes in activity levels and patterns

may influence how and which homeostatic mechanisms are engaged. Additionally, if a cell does engage multiple mechanisms, the order of engagement and further interactions between mechanisms remains unresolved. Multiple studies suggest that the reduction of inhibition levels occurs immediately after sensory deprivation (Chen et al., 2011; Hengen et al., 2013; Keck et al., 2011; Kuhlman et al., 2013; Li et al., 2014; van Versendaal and Levelt, 2016), but the consequences for subsequent homeostatic or Hebbian mechanisms is not clear. Consequently, it is an important future topic to explore how individual mechanisms, as well as their interactions, affect behavior. For example, at a mechanistic level, while TNF-alpha knock-out mice show clear abnormalities in sensory responses (Greenhill et al., 2015; Kaneko et al., 2008b), it is yet to be explored if this affects behaviors requiring sensory acuity. At a more general level, it is intriguing to explore the interaction between different mechanisms, as they can compensate for each other (Marder and Goaillard, 2006) and their combination can achieve a non-trivial functional outcome.

In addition to the interactions among the homeostatic mechanisms themselves, the relationship between the Hebbian and homeostatic mechanisms is not particularly well understood. Following monocular deprivation, circuit reorganization is proposed to occur via LTD (Rittenhouse et al., 1999) followed by the homeostatic mechanism of either synaptic scaling (Stryker Position Paper in this issue) or changing the sliding threshold to favor LTP (Cooper and Bear, 2012), but whether homeostatic mechanisms are only engaged after the cell has induced Hebbian plasticity past some threshold (as may be the case with monocular deprivation) or if these homeostatic mechanisms are constantly at work to never allow activity to get too far out of range is unclear. One issue in the field is that given the sensitivity of the currently used experimental approaches, one needs to induce a strong change in activity or a significant loss of input in order to be able to measure that homeostatic mechanisms have been engaged. With the advent of new, more sensitive tools to both manipulate activity (light-activated channels) and measure activity (voltage sensitive dyes), these questions will likely be resolved in the near future. Finally, while numerous molecules have been identified to play a role in mechanisms of both types of

plasticity, there is overlap between these molecular cues (Vitureira and Goda, 2013). The interactions between the molecular mechanisms of Hebbian and homeostatic plasticity are largely unexplored and are an important question for identifying how these different types of plasticity are induced.

The study of homeostatic plasticity would also be greatly advanced by the development of genetic and pharmacological methods for regulating and preventing it. Hebbian plasticity can be controlled genetically by numerous interventions, from manipulating NMDA receptors through CaM-kinase-II-alpha to scaffolding mechanisms involved in receptor trafficking, and pharmacologically by AP5 and CPP. Experimental manipulation of homeostatic scaling has been achieved principally by genetic or pharmacological alteration of TNF-alpha signaling; no selective manipulation is yet known for regulation of inhibition. It will be important for advances in the molecular understanding of homeostatic plasticity mechanisms to lead to additional tools that can be employed *in vivo* and targeted to specific cells. Without such tools, it will be difficult to dissect the interaction of these two forms of plasticity further and make better connections with theoretical studies.

To conclude, the ideas that emerged at this meeting reinforced many of the general concepts that have evolved over the past fifteen to twenty years– the mechanisms of homeostatic plasticity (synaptic scaling, changes in inhibition), the recovery of activity following input loss and the necessity for some form of stability to balance Hebbian changes. Clear directions for future research, together with important experiments going forward include 1) understanding the relevant time scales for both homeostatic and Hebbian changes and how stability in the circuit can be maintained despite these differences in time scales, 2) more effectively connecting theory with molecular and systems level experiments, 3) understanding the spatial scales of both the set points that the cells and networks are trying to achieve and the implementation of plasticity mechanisms, 4) characterizing the interactions, both spatial and temporal, between mechanisms of homeostatic and Hebbian plasticity and if the effector molecules are the same for these two forms of plasticity, 5) understanding the

molecular mechanisms for the three types of homeostatic plasticity – synaptic scaling, modulation of inhibition and firing rate homeostasis, and 6) understanding the temporal, spatial and mechanistic dynamics of the understudied synaptic down-scaling.

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